ANTISENSE OLIGONUCLEOTIDES TARGETING TIA1

SEQUENCE LISTING

[0001] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Mar. 29, 2021 is named 51551-006001_Sequence_Listing_03.29.21_ST25 and is 156,502 bytes in size.

FIELD OF INVENTION

[0002] The present invention relates to antisense oligonucleotides (oligomers) complementary to nucleic acids encoding mammalian T cell-restricted intracellular antigen-1 (TIA1), in particular antisense oligonucleotides targeting TIA1 pre-mRNA sequences, which are capable of inhibiting the expression of TIA1. Inhibition of TIA 1expression is beneficial for a range of medical disorders including neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS), Frontotemporal Dementia, and tauopathies.

BACKGROUND

[0003] One of the hallmarks of many neurodegenerative diseases is the accumulation of protein inclusions in the brain and central nervous system. These inclusions are insoluble aggregates of proteins and other cellular components that cause damage to cells and result in impaired function. Proteins such as tau, alpha-synuclein, huntingtin and P-amyloid have all been found to form inclusions in the brain and are linked to the development of a number of neurodegenerative diseases, including Alzheimer's disease and Huntington's disease. Neurodegenerative diseases are also associated with stress granules, which contain RNAs and aggregated RNA binding proteins.

[0004] T cell-restricted intracellular antigen-1 (TIA-1) is an RNA binding protein and a core nucleating stress granule protein. In stress granule formation, nucleation is followed by recruitment of secondary RNA-binding proteins to form a mature stress granule, which is a key component of stress-induced translational suppression. TIA1 co-localizes with neuropathology in the brain tissue of subjects with neurodegenerative disorders (see for example Maziuk et al., Acta Neuropathologica Communications 2018 6:71). Appicco et al., Nat Neurosci. 2018 Jan; 21(1):72-80 reports that reducing the RNA binding protein TIA1 protects against tau-mediated neurodegeneration in vivo.

[0005] Amyotrophic lateral sclerosis (ALS) is a complex neurodegenerative disease, characterized genetically by a disproportionately large contribution of rare genetic variation. Driven by advances in massive parallel sequencing and applied on large patient-control cohorts, systematic identification of these rare variants that make up the genetic architecture of ALS became feasible (Nguyen et al., Trends in Genetics June 2018, Vol. 34, No. 6). Mackenzie et al., Neuron 95, 808-816, Aug. 16, 2017 reports that mutations affecting the low-complexity domain of TIA1 cause Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD) ALS and ALS-FTD and that ALS-linked TIA1 mutations share a neuropathological TDP-43 signature, that TIA1 mutations promote phase separation and impair stress granule dynamics, and that TDP-43 recruited to poorly dynamic stress granules becomes immobile and insoluble attributing to disease. Hirsch-Reinshagen et al. Acta Neuropathologica Communications (2017) 5:96 discloses clinical and widespread TDP-43 neuropathological features of ALS/FTD with Tia1 mutations.

[0006] WO 2017/066657 refers to nucleic acid based inhibitors of TIA1.

OBJECTIVE OF THE INVENTION

[0007] The inventors have identified particularly effective regions of the TIA1 transcript (TIA1) for antisense inhibition in vitro or in vivo, and provides for antisense oligonucleotides, including LNA gapmer oligonucleotides, which target these regions of the TIA1 prem RNA or mature mRNA. The present invention identifies oligonucleotides which inhibit human TIA1 which are useful in the treatment of a range of medical disorders including neurological disorders, particularly nuerological disorders associated with stress granule formation.

STATEMENT OF THE INVENTION

[0008] The invention provides for an antisense oligonucleotide, 10-30 nucleotides in length, targeting a human TIA1 target nucleic acid. The invention provides a range of novel target sites within the human TIA1 pre-mRNA, and further provides for antisense oligonucleotides which comprise at least 10 or more contiguous nucleotides which are complementary to such a novel target site. The antisense oligonucleotides of the invention are capable of inhibiting the expression of human TIA1 in a cell which is expressing human TIA1.

[0009] The invention provides for an antisense oligonucleotide, 10-30 nucleotides in length, targeting a human TIA1 target nucleic acid, wherein the antisense oligonucleotide is capable of inhibiting the expression of human TIA1 in a cell which is expressing human TIA1.

[0010] The invention provides for an antisense oligonucleotide, 10-30 nucleotides in length, targeting a human TIA1 target nucleic acid, wherein said antisense oligonucleotide comprises a contiguous nucleotide sequence 10-30 nucleotides in length, wherein the contiguous nucleotide sequence is at least 90% complementary, such as fully complementary, to a sequence selected from the group consisting of SEQ ID NO 4-53.

[0011] The invention provides for an antisense oligonucleotide, 10-30 nucleotides in length, targeting a human TIA1 target nucleic acid, wherein said antisense oligonucleotide comprises a contiguous nucleotide sequence 10-30 nucleotides in length, wherein the contiguous nucleotide sequence is at least 90% complementary, such as fully complementary to a region of SEQ ID NO 1 selected from the group consisting of (target sequence regions—identified by their nucleotide position range in SEQ ID NO 1)-LIST A: 8-23; 33-52; 54-96; 103-139; 148-162; 164-195; 212-358; 360-393; 403-423; 456-478; 491-507; 509-538; 571-606; 604-627; 637-658; 660-685; 687-712; 714-729; 744-765; 792-843; 845-873; 875-916; 931-950; 955-971; 973-991; 1003-1029; 1045-1081; 1083-1101; 1105-1150; 1153-1288; 1297-1318; 1331-1368; 1370-1389; 1391-1465; 1482-1521; 1523-1557; 1557-1579; 1591-1605; 1613-1669; 1678-1698; 1743-1787; 1789-1816; 1822-1855; 1860-1892; 1901-1918; 1908-1929; 1919-1961; 1964-1987; 1978-2002; 2004-2018; 2020-2049; 2038-2052; 2048-2068; 2070-2086; 2088-2115; 2117-2134; 2136-2166; 2167-2207; 2209-2224; 2228-2260;